

## Tetracyclines\*

### Overview

Tetracyclines are the third most widely prescribed antibiotic class in the world. The first tetracycline antimicrobial, aureomycin, was discovered in 1948 by an American botanist, Benjamin Minge Duggar. Duggar's interest was the study of molds found in soil. One such mold was discovered to have antibiotic properties against bacilli, streptococci, staphylococci and a host of other organisms. The name aureomycin comes from the Latin word "aureus", meaning gold, reflecting the golden hue of the substance, and the Greek word "mykes", meaning mold, referring to the substance's origin. Examples of tetracyclines presently available in the United States are tetracycline, oxytetracycline, doxycycline and minocycline. The primary mechanism of action of tetracyclines is suppression of protein synthesis by reversible binding to the 30S ribosomal subunit which results in blocking the attachment of transfer RNA to the messenger RNA ribosomal complex. Tetracycline exerts the same effect on mammalian cells, but bacterial cells are selectively more susceptible. Tetracyclines are bacteriostatic, requiring a responsive host defense mechanism, and exhibit a broad spectrum of activity against many different aerobic and anaerobic bacteria, including *Rickettsiae*, *Chlamydiae*, mycoplasmas, spirochetes, mycobacteria and some protozoa, including *Plasmodium falciparum*. Tetracyclines tend to be more effective against multiplying organisms and are more active at a pH of 6-6.5.

Tetracyclines are crystalline, yellowish substances that can behave as either an acid or base. In aqueous solution they form salts with both acids and bases and do not remain stable, especially at high pH. For this reason parenteral preparations are carefully formulated in either propylene glycol or pyrrolidone. Dispersing agents are added to stabilize the solutions. Tetracyclines fluoresce when exposed to ultraviolet light.

Thirty-three independent *tet* genes conferring resistance to tetracyclines have been identified. Most are components of mobile genetic elements. Microbial resistance to tetracyclines is usually characterized by decreased penetration of the drug into organisms that were once susceptible. Some resistant mutants lack the necessary transport system, an energy dependent system that brings about high intracellular levels of the drug in susceptible bacteria. *Pseudomonas aeruginosa* and *Staphylococcus aureus* can acquire resistance to tetracyclines by acquisition of the *tet* gene either by plasmid transfer or on a chromosome. The mechanism of this type of resistance is drug efflux and often results in resistance to tetracycline and doxycycline, but not minocycline. An additional mechanism of tetracycline resistance is alteration of the target ribosome site. Ten of the 33 *tet* genes encode ribosome-modifying enzymes that confer resistance to tetracycline, doxycycline and minocycline. Resistance develops slowly but is usually widespread due to extensive use of low levels of the tetracyclines. Cross resistance among the tetracyclines does occur. Frequently some strains of *Pseudomonas aeruginosa*, *Proteus*, *Serratia*, *Klebsiella* and *Corynebacterium* species are resistant to tetracyclines.

Tetracycline absorption in the gastrointestinal tract can be impaired by sodium bicarbonate, aluminum hydroxide, magnesium hydroxide, iron, calcium salts, milk and other dairy products. Therefore in addition to milk, antacids and kaolin products reduce

absorption. Tetracyclines are distributed well throughout the body achieving high concentrations in the kidneys, liver, bile, lungs, spleen and bone. Lower levels are found in serosal fluids, synovia, cerebrospinal fluid, ascitic fluid, prostatic fluid and vitreous. Tetracyclines chelate calcium ions and are deposited irreversibly in growing bone and in the enamel of un-erupted teeth. Tetracyclines are metabolized in the liver. This class of drugs and their metabolites are excreted primarily in urine. Doxycycline, however, is the exception; most of the drug and its metabolites are excreted in the feces.

Oral tetracyclines at therapeutic levels should never be administered to ruminants due to depression of ruminal microflora. Buffered tetracyclines can be administered intramuscularly and intravenously, however tissue necrosis at injection sites is common. Hypersensitivity reactions can occur with administration of tetracyclines. This can appear in cats as a “drug fever” reaction with vomiting, diarrhea, lethargy, inappetence and eosinophilia. Nausea, vomiting, anorexia and “unpleasant taste” can occur with tetracycline use in humans. Other side effects include reduction of vitamin B and vitamin K availability from the gut, inhibition of bone healing, hypotension or intravascular hemolysis with intravenous administration of some tetracycline preparations, hepatotoxicity (especially in pregnancy), nephrotoxicity, increased intracranial pressure, photosensitivity, inhibition of the immune system (especially with concurrent glucocorticoid use), superinfection with *Candida* species and, of course, discoloration and hypoplasia of tooth enamel. Tetracycline use is not recommended in immature patients with un-erupted teeth or in pregnancy, due to effects on enamel.

Besides the problem with milk, antacids and kaolin preparations, interactions with other substances may cause physiologic problems. An increase in occurrence of nephrotoxicity is observed when tetracyclines are used with methoxyfluorane anesthesia.

**\*References available by request. Call the Infectious Disease Epidemiology Section, Office of Public Health, Louisiana Department of Health and Hospitals (504-219-4563)**